Cost-Effectiveness of Implantable Pulmonary Artery Pressure Monitoring in Chronic Heart Failure

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Objectives

This study aimed to evaluate the cost-effectiveness of the CardioMems device in patients with chronic heart failure.

Background

The CardioMems device, an implantable pulmonary artery pressure monitor, was shown to reduce heart failure hospitalizations and improve quality of life in the CHAMPION trial.

Methods

We developed a Markov model to determine the hospitalization, survival, quality of life, cost, and incremental cost-effectiveness ratio of CardioMems implantation compared with usual care among a CHAMPION trial cohort of heart failure patients. We obtained event rates and utilities from published trial data; we used costs from literature estimates and Medicare reimbursement. We performed subgroup analyses of preserved and reduced ejection fraction and an exploratory analysis in a lower-risk cohort based on the CHARM trials.

Results

CardioMems reduced lifetime hospitalizations (2.18 versus 3.12), increased QALYs (2.74 versus 2.46) and increased costs ($176,648 versus $156,569), yielding a cost of $71,462 per QALY gained and $48,054 per life-year gained. The cost per QALY gained was $82,301 in patients with reduced ejection fraction and $47,768 in those with preserved ejection fraction. In the lower-risk CHARM cohort, the device would need to reduce heart failure hospitalizations by 41% in order to cost less than $100,000 per QALY gained. The cost-effectiveness was most sensitive to the device's durability.

Conclusion

In populations similar to the CHAMPION trial, the CardioMems device is cost-effective if the trial effectiveness is sustained over long periods. Post-marketing surveillance data on durability will further clarify its value.

Key Words

Heart failure, monitoring, cost-effectiveness, CardioMems, technology

Abbreviations

ACC/AHA: American College of Cardiology/American Heart Association

AHRQ: Agency for Health Research and Quality

CHAMPION trial: CardioMems Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients trial

CHARM trials: Candesartan in Heart failure: Reduction in Mortality and morbidity trials

CPT: Current Professional Technologies

MLWHF: Minnesota Living with Heart Failure

NYHA: New York Heart Association

QALYs: Quality-adjusted life years

USD: United States Dollars

Heart failure treatment costs over $20.9 billion in total healthcare expenditures.(1) Most of these costs are incurred from treating clinical decompensations of patients with heart failure that result in over 1 million hospital admissions annually.(1,2) The CHAMPION trial, a randomized, single-blinded, multicenter trial, investigated the use of an implantable, wireless pulmonary artery pressure monitoring system to decrease heart-failure-related hospitalizations.(3) In this study, 550 patients with NYHA Class III heart failure and a heart failure hospitalization within the previous year underwent pulmonary artery sensor implantation. Patients were randomized to a treatment group in which providers were given access to the pressure readings or a control group in which the provider could not access the pressure readings. The treatment group was found to have fewer heart failure hospitalizations and improved quality of life.

New management strategies such as CardioMems that reduce costly heart failure hospitalizations may decrease the substantial clinical and economic burden of heart failure. However, the high device cost (listed as $17,750 with Medicare) raises questions regarding its value.(4) We performed an independent analysis of the cost-effectiveness of this device in a cohort based on the trial, as well as in subgroups defined by ejection fraction. Additionally, we performed an exploratory analysis of the device in an alternative, larger trial-based cohort of heart failure patients using the CHARM trials.(5)

METHODS

Decision model

We developed a Markov model to determine the cost-effectiveness of the CardioMems device compared with usual care from a societal perspective in a CHAMPION trial cohort over a lifetime horizon. This included adults (average age of 62) with NYHA Class III heart failure, hospitalized within 1 year with preserved (21.7%) or reduced ejection fraction (78.3%). We used

hospitalization and mortality rates from the CHAMPION trial.(3) We performed subgroup analyses of reduced ejection fraction (average age of 60) and preserved ejection fraction (average age of 66) cohorts from the CHAMPION trial utilizing overall trial event rates and subgroup-specific rate ratios for each event from trials with larger sample sizes than CHAMPION.(6-9) Subgroup-specific device efficacy was extracted from the CHAMPION trial.(3)

In the model, individuals had CardioMems device placement at the outset, which could involve a procedural complication or device deployment failure. In subsequent monthly intervals, individuals could experience heart failure hospitalizations, non-heart failure hospitalizations, device complications, and all-cause mortality (Supplement Figure S1). Individuals had an increased mortality risk during the heart failure hospitalization and for two months post-hospitalization. The model followed all patients over their lifetimes. We matched the mortality rates over the mean duration of the trial for the control arm of the CHAMPION trial (17 months). After the trial period of 17 months, all event rates are extrapolated. We extrapolated an age-based increase in overall mortality from a previous retrospective analysis.(10)

Heart failure hospitalization rate and efficacy of the CardioMems device

We matched the trial rates of hospitalizations secondary to heart failure for each cohort. We modeled a declining rate of hospitalization over the CHAMPION trial duration. We modeled the CardioMems reduction in the rate of heart failure hospitalizations on the reduction over the entire trial (hazard ratio 0.63). We assumed that preventing a hospitalization prevented an inpatient and a two-month post-hospitalization increase in mortality.(11-13) We did not model any additional CardioMems-associated mortality reduction in the base case. For our base case, we assumed the benefit of the CardioMems device would continue lifelong, and examined shorter durations in sensitivity analyses.

CardioMems device events

We modeled periprocedural complications as a composite of the procedure-related serious adverse events and major bleeding during the thirty-day post-procedure anticoagulation period.(3) We additionally modeled procedural placement failure and CardioMems-related serious adverse events that occurred after the initial month.

Quality of life and costs

We included quality of life estimates for the patient's baseline health, the use of the CardioMems device, hospitalizations, and complications using utilities. We calculated utility values by converting the 6-month Minnesota Living with Heart Failure (MLWHF) questionnaire score for the control arm in the CHAMPION trial into EQ-5D scores.(14) The difference-in-difference in EQ-5D score between groups from baseline to 6 months was applied as the quality of life benefit for the CardioMems device for the first year. The difference-in-difference between groups from baseline to 12 months was applied thereafter. The six-month differences were utilized for the entire first year because 226 of 550 patient scores were missing at 12 months. Disutilities were applied for the initial procedure, hospitalizations, and complications. Comparisons of patient utility during and after a heart failure hospitalization showed an 11% lower utility during hospitalization, for a decrement of approximately 3 days.(15) These assumptions were tested in sensitivity analyses, including an analysis in which we alternatively assumed long-term utility change secondary to heart failure hospitalizations.(16)

We included all healthcare-related costs. Hospitalization costs were taken from the AHRQ National Inpatient Sample(17) with physician costs calculated using the 2014 Medicare Professional Fees (CPT Codes 99212, 992213, 99222, 99223, 99254, and 99255).(18) Age-adjusted outpatient medical costs for patients with heart failure were taken from the literature.(2)

The cost of CardioMems implantation, in addition to the device cost, is the cost for the right heart catheterization and angiography ($1,129) (from base Medicare 2014 Professional Fees, CPT Codes 93451 and 93568) along with the fee for device placement, currently an unlisted fee, which we assumed would approximate that of inserting a temporary single chamber cardiac electrode ($185, Medicare CPT 33210).(18,19) This assumption was based on selecting reimbursement for a simple intracardiac procedure given this is additional to catheterization and angiography reimbursement. We based the monthly cost of CardioMems management on the estimated time required to monitor the device by physicians and nurses and average provider wage.(20,21,Klein L, personal communication, November 2015) All costs were updated to 2014 USD using the medical component of the consumer price index.(22)

Sensitivity analyses

We evaluated the effect of uncertainty in all model inputs (Table 1). We focused on device-specific uncertainties and characteristics of the patient population. Given the single clinical trial currently available, we varied estimates of the efficacy of the device extensively by adjusting the reduction in hospitalizations, the effect of the device on mortality, the effect on quality of life, and the duration of the device's effectiveness. With its recent market introduction, we also varied the costs of the device, implantation, and monitoring substantially. Given the large heterogeneous heart failure population, we also conducted analyses on a range of hospitalization costs, baseline utility values, and baseline hospitalization and mortality rates. This included an exploratory analysis of the intervention in a cohort based on the CHARM trials, which was a lower-risk cohort with greater quality-of-life and lower event rates. This cohort included adults (average age of 62) with NYHA Class II (45%), Class III (52%) and Class IV (3%) heart failure, as opposed to patients in CHAMPION who exclusively had NYHA Class III disease. We used

published CHARM trial data to estimate hospitalization and mortality rates along with utility scores.(5,6,23) We adjusted the rates to match the ejection fraction subgroup composition of the CHAMPION cohort and to include only patients with a previous heart failure hospitalization. We estimated the device effectiveness needed to meet important cost-effectiveness thresholds in this cohort.

We performed a probabilistic sensitivity analysis by performing 10,000 simulations in which we simultaneously sampled from the distributions of each input parameter with each simulation (Supplement for details).

We discounted future costs and benefits at 3% annually, and adhered to best practices.(24,25) The main outcome measure was cost per QALY gained. Cost-effectiveness thresholds followed ACC/AHA guidelines, with a threshold of less than $50,000 indicating highly cost-effective and greater than $150,000 not cost-effective.(26)

RESULTS

Comparison to the CHAMPION trial results

In the first six months, modeled rates of hospitalizations per patient-six months for the usual care and the intervention groups of 0.44 and 0.29 matched the CHAMPION trial's 0.44 (CI 0.36-0.53) and 0.32 (0.26-0.40). The modeled annual rates over the mean trial period for the two groups were 0.68 and 0.45, matching trial results of 0.69 (0.61-0.78) and 0.46 (0.40-0.53). The modeled annual mortality probabilities over the mean trial period for the usual care and intervention groups were 14.8% and 13.2% matching the trial's 14.7% (11.7-17.9) and 11.9% (9.5-16.3). Further details are included in the Supplement.

Base Case

In the CHAMPION trial cohort, the modeled CardioMems arm has a total of 2.18 hospitalizations per patient compared to 3.12 in the usual care arm, an absolute reduction of 0.94 hospitalizations over a patient's lifetime (Table 2). The CardioMems arm increased life expectancy by 0.42 years and quality-adjusted life expectancy by 0.28 QALYs. The CardioMems arm achieved its health benefits at an increased cost of $20,079. Taken together, the CardioMems intervention costs $71,462 per QALY gained or $48,054 per life-year gained.

Ejection fraction subgroups

Patients receiving usual care in the preserved ejection fraction subgroup had a longer average survival than the reduced ejection fraction subgroup (Table 2). The reduction in hospitalizations with CardioMems was greater for patients with preserved ejection fraction compared with those with reduced ejection fraction, which also resulted in lower incremental costs. With more QALYs gained and a smaller difference in costs, CardioMems cost $47,768 per QALY gained in the preserved ejection fraction cohort compared to $82,301 in the reduced ejection fraction cohort.

Costs

The base case used a device cost of $17,750. The device cost less than $50,000 per QALY gained if the cost is less than $9,798 in those with reduced ejection fraction and less than $18,657 in those with preserved ejection fraction (Figure 1). Use of the device would cost more than $150,000 per QALY gained if it cost more than $34,418 in the reduced ejection fraction subgroup or $59,296 in the preserved ejection fraction subgroup. The cost of a heart failure hospitalization ($12,832) was based on the national average; however, there is significant hospital variation. In a large, urban, public, teaching hospital with a higher predicted cost of hospitalization ($16,750), the CardioMems device costs $62,121 per QALY gained. In a small,

rural, private, non-teaching hospital with lower predicted costs of hospitalization ($8,341) the device becomes less favorable, costing $82,169 per QALY gained (Figure 2).

In the base case, we assumed a monthly cost of $68 to monitor the CardioMems device. This cost would need to be under $190 monthly for the device to cost less than $100,000 per QALY and below $403 monthly for a cost less than $150,000 per QALY.

Device efficacy

The efficacy of the CardioMems device is modeled via reduction in hospitalizations, the risk of mortality associated with hospitalizations, and the effect on baseline quality of life. While CardioMems had a 0.63 hazard ratio for hospitalizations over the entire randomized period of the CHAMPIONS trial, the confidence interval was 0.52-0.77. Over this range, CardioMems costs between $52,556 and $120,143 per QALY gained. The effect of the CardioMems device on mortality is uncertain. In the base case, we assumed that prevented hospitalizations had a similar inpatient mortality risk to all heart failure hospitalizations and that preventing these hospitalizations would also avert the associated increase in post-hospitalization mortality, which led to an 11% relative reduction in mortality in the CardioMems arm compared with usual care over the trial period. If we had instead assumed a 20% relative reduction, the value of the CardioMems device would improve to $55,378 per QALY gained. However, if preventing hospitalizations did not reduce mortality, the cost would be $159,984 per QALY gained. For the device to cost less than $100,000 per QALY gained, the relative reduction in mortality must be at least 4%.

Though the CHAMPION trial followed patients for 17 months on average, we assumed a lifelong duration. If CardioMems' effectiveness ceased after 17 months, its cost per QALY gained was $214,879. Cost per QALY gained declined as the duration of effectiveness increased,

dropping below $150,000 at 34 months and $100,000 at 72 months. In two-way sensitivity analyses, we found that the device is much less cost-effective if its duration of effect is shorter in populations with lower monthly hospitalization rates (Figure 3).

Adjusting the peri-procedural complication rate, chronic complication rate, or placement failure rate did not substantially alter our findings (Supplement).

Utilities

The impact of the CardioMems device on quality of life did not substantially change our main findings (Supplement). Neither alternative assumptions of baseline utility nor duration of disutility from hospitalization substantially altered our results (Supplement). Adjusting long-term baseline utility based on the number of heart failure hospitalizations also did not substantially affect our findings (Supplement).

Severity of illness

Baseline rates of hospitalization and mortality matched trial rates. However, individual healthcare systems will have heterogeneous patient groups with different rates of readmission and mortality. We found decreases to the hospitalization rate and increases to the mortality rate both increased the cost per QALY of CardioMems, but the cost did not exceed $150,000 per QALY gained (Supplement Figure S2).

In the CHARM cohort, the usual care arm had greater survival (7.9 years), more QALYs (4.67), and fewer heart failure hospitalizations (1.71) compared with the CHAMPION cohort. If the device had a similar effect on quality of life in the CHARM cohort as in the CHAMPION trial, the device would need to prevent 26.5% of failure hospitalization to cost less than $150,000 per QALY gained and 41.1% to cost less than $100,000 per QALY gained (Supplement Figure S3).

Time horizon

In the base case, we used a lifetime horizon. Over a five-year horizon, which was used in the trial cost-effectiveness, we found a $15,029 difference in costs and a 0.11 difference in QALYs, yielding a cost of $138,466 per QALY gained (Supplement Figure S4).

Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis, we found 17.3% of simulations showed CardioMems was the preferred intervention at a willingness-to-pay threshold of $50,000, 76.9% at a threshold of $100,000 and 95.1% at a threshold of $150,000 (Supplement Figure S5). Additional sensitivity analyses are available in the Supplement.

DISCUSSION

Our analysis demonstrates that the use of the CardioMems device is cost-effective in patients with NYHA Class III heart failure and a history of heart failure hospitalization in the preceding year. Our base case analysis finds a cost of $71,462 per QALY gained in a CHAMPION trial population. The device value is most sensitive to its durability and the association between the reduction in hospitalizations and survival. The device must provide benefits over at least 34 months to cost less than $150,000 per QALY. With randomized data of 17 months and open-access data for an additional 13 months, the device's effectiveness over a longer period is unknown. Although heart failure hospitalizations are associated with an increased mortality risk, it is unclear how preventing hospitalizations with CardioMems affects survival. The CHAMPION trial was underpowered to detect a mortality difference; a survival analysis submitted to the FDA demonstrated substantial uncertainty (HR 0.8, CI: 0.55-1.15). We demonstrate that the device would need to reduce mortality by 4% to cost less than $100,000 per QALY. While this seems likely, it is possible that prevented hospitalizations may be lower risk and mortality may be relatively unaffected. Future studies that follow hospitalization trends and

refine estimates of the effect of the device on mortality can reduce the uncertainty regarding its clinical and economic value.

Our analysis indicates that the CardioMems device provides better value in patients with preserved ejection fraction. There are few evidence-based treatments available for patients with preserved ejection fraction; thus, the CardioMems device represents a rare evidence-supported intervention for this important group. Our model predicted greater value in this group due to the longer survival and increased device effectiveness in this group; however, the estimate of effectiveness in this group is based on only 119 trial patients and should also be refined with future research.

The incremental cost-effectiveness ratio found in the CHAMPION trial was more favorable than our estimate.(3) Their study, performed over a five-year time horizon, found a larger difference in QALYs and a much smaller cost difference between the two arms ($4,282) to lead to an incremental cost-effectiveness of $13,379 per QALY. We do not have access to their assumptions to analyze these differences. The lifetime horizon used in our model captures longer-term benefits and costs and the impact of device durability.

The importance of the CardioMems device is tied to the scope of the problem. Healthcare expenditures secondary to heart failure are expected to rise from $20.9 billion in 2012 to $53.1 billion in 2030, with 80% of these costs attributed to heart failure hospitalizations.(27) These hospitalizations are not only costly but also markers of a worsening clinical prognosis, being associated with high rates of rehospitalization and mortality. Strategies to reduce this clinical and economic burden are needed. We demonstrate that the CardioMems device may be a cost-effective intervention for outpatient heart failure management. However, our analysis also shows that the savings from reduction in hospitalization costs are exceeded by the intervention costs,

which could thereby still have a large budgetary impact. We also illustrate the value decreases in lower risk patients; with the substantial heterogeneity in morbidity of heart failure patients, ensuring patients fit the trial criteria will be important. Although it is a costly intervention that should be reserved for appropriately selected patients and still requires further evaluation, the value of this device compares favorably to other technologies used in similar patient groups, such as left-ventricular assist devices.(28)

Study limitations

There are a number of limitations to our analysis. First, a single trial has evaluated the intervention; the effectiveness seen in this trial should be confirmed in post-surveillance evaluation. Second, there may be treatment benefits that are not captured in our model, such as identifying patients who need to initiate advanced therapy. Third, although there were no serious device-related complications outside of the procedural period, long-term safety data is not currently available. Finally, we attempted to capture additional costs of using the device using the time required at a heart failure center, but the average national cost of the monitoring program is currently unclear.

Conclusions

This analysis shows that the use of the CardioMems device is a cost-effective means of improving heart failure quality of life and reducing rehospitalizations. It is a better value in patients with preserved ejection fraction, a group with few effective therapies. The cost-effectiveness of CardioMems is most sensitive to the duration of effectiveness; therefore, further research on the continued hospitalization trends of patients with the device will be important for future evaluations.

Clinical Perspectives

In patients with NYHA Class III heart failure and a heart failure hospitalization in the preceding year, the CardioMems device reduced heart failure readmissions and improved quality of life at a cost below commonly accepted U.S. willingness-to-pay thresholds. The device was cost-effective for both patients with reduced ejection fraction and preserved ejection fraction.

Translational Outlook

The clinical effectiveness of the device has only been demonstrated in a single randomized clinical trial with a mean follow-up of 17 months. Evaluation of the long-term heart failure hospitalization rate and the relationship between averted hospitalizations and changes in mortality in individuals after CardioMems implantation will refine estimates of the value of the device. Additional data regarding the cost of maintaining and monitoring the device in the community will also inform future economic evaluations.

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Figure 1. Cost-effectiveness of CardioMems as a function of device cost

This one-way sensitivity analysis demonstrates the effect of the price of the CardioMems device on its cost-effectiveness in both the CHAMPION cohort and the preserved EF and reduced EF subgroups.

Figure 2. Tornado Diagram: series of one-way sensitivity analyses

The bars indicate the range of cost per QALY gained with the CardioMems device compared with usual care in 1-way sensitivity analyses of the input parameters across the range of values, listed to the left and right of the bars. The above variables were selected because they had the largest effect on the cost-effectiveness ratio of the device. The solid line demonstrates the cost-effectiveness in the CHAMPION cohort of $71,462 per QALY gained. The dotted line represents the cost-effectiveness threshold of $150,000 per QALY gained.

Figure 3. Cost-effectiveness of CardioMems device as a function of hospitalization risk and duration of device effect

This graph is a two-way sensitivity analysis of the monthly rate of heart failure hospitalizations and the duration of clinical effect. The probability of heart failure hospitalizations has been varied and the average monthly rate of hospitalizations (discounted) of the usual care arm has been displayed on the y-axis. The duration that the CardioMems device is assumed to function (years) is on the x-axis. The colored lines represent the cost per QALY gained at that point. The cost per QALY gained decreased with increases in the hospitalization rates and the duration of effectiveness. The red dotted horizontal line displays the base case hospitalization rate (4.3%). The black vertical dotted line is the average patient follow-up in the CHAMPION study (17 months).

Table 1. Selected Input Parameters[*]

	Base Case	Range	Source
Event Probabilities (Monthly)[†]			
CHAMPION cohort			
Baseline All-Cause Mortality (%)[‡]	0.99	0.66-1.31	(3)
Baseline Heart Failure Hospitalization (HFH)(%)[§]	8.76	4.38-13.15	(3)
Inpatient HFH Mortality (%)	3.90	3.60-4.20	(11,12)
Relative Risk of Death after HFH[**]	3.32	1.00-4.98	(13)
Non-heart Failure Hospitalization (%)	8.30	6.99-9.60	(3)
Relative Risk (RR) of Preserved Ejection Fraction (pEF) Subgroup, compared to Reduced Ejection Fraction (rEF) Subgroup			
RR of All-Cause Mortality, pEF vs. rEF	0.52	0.43-1.00	(6-9)
RR of HFH, pEF vs. rEF	0.64	0.54-1.00	(6-9)
RR of HFH Inpatient Mortality, pEF vs. rEF	0.74	0.67-1.00	(6-9)
CHARM Cohort[††]			
Heart Failure Mortality (%)[‡‡,‡]	0.66	0.43-0.89	(5,6)
Baseline HFH (%)[‡‡,§]	3.11	2.32-3.89	(5,6)
CardioMems Arm Specific Parameters			
RR of HFH, compared to usual care	0.63[§§]	0.52-0.77	(3)

Placement Failure (%)	4.35	2.68-6.01	(3)
Costs ($)			
Cost of Heart Failure Hospitalization	12,832	8,341-16,750	(17)
Cost of CardioMems Device	17,750	8,875-35,500	(4)
Cost of CardioMems Placement[***]	1,129	564-2,258	(4,19)
Monthly Cost of CardioMems Device Management	68	34-136	[†††]
Utilities			
Baseline Utility, CHAMPION Cohort[‡‡‡]	0.55	0.51-0.75	(3,14)
Baseline Utility, CHARM Cohort[‡‡‡]	0.66	0.64-0.68	(14,23)
Disutility of Heart Failure Hospitalization	0.059	0-0.11	(15)
Utility of CardioMems Device for first 12 months[‡‡‡]	0.010	0-0.019	(3,14,15)
Utility of CardioMems Device after first 12 months[‡‡‡]	0.004	0-0.019	(3,14,15)

[*] Abbreviations: HFH: heart failure hospitalizations; RR: relative risk; pEF: preserved ejection fraction; rEF: reduced ejection fraction; MLWHF: Minnesota Living with Heart Failure.

[†] Listed probabilities refer to the probabilities for patients with rEF. Probabilities of pEF calculated via the RR between pEF and rEF groups.

[‡] Adjusted for age with an exponential model (Supplement for further details).

[§] Heart failure hospitalization probability adjusted by a monthly decreasing exponential model based on model stage to adjust for decreasing hospitalization rate with increasing time from initial hospitalization. This was set as constant after 17 months (Supplement for further details).

[**] Increased risk for two months prior to returning to baseline.

[††] Only differed from CHAMPION cohort with regards to hospitalization probability, mortality probability, and baseline quality of life. Used the same exponential models as CHAMPION cohort to adjust hospitalization and mortality probabilities.

[‡‡] Estimated from patients from all three CHARM trials and adjusted for those with a previous HFH and ejection fraction composition.

[§§] rEF subgroup RR of 0.67; pEF subgroup RR of 0.48.

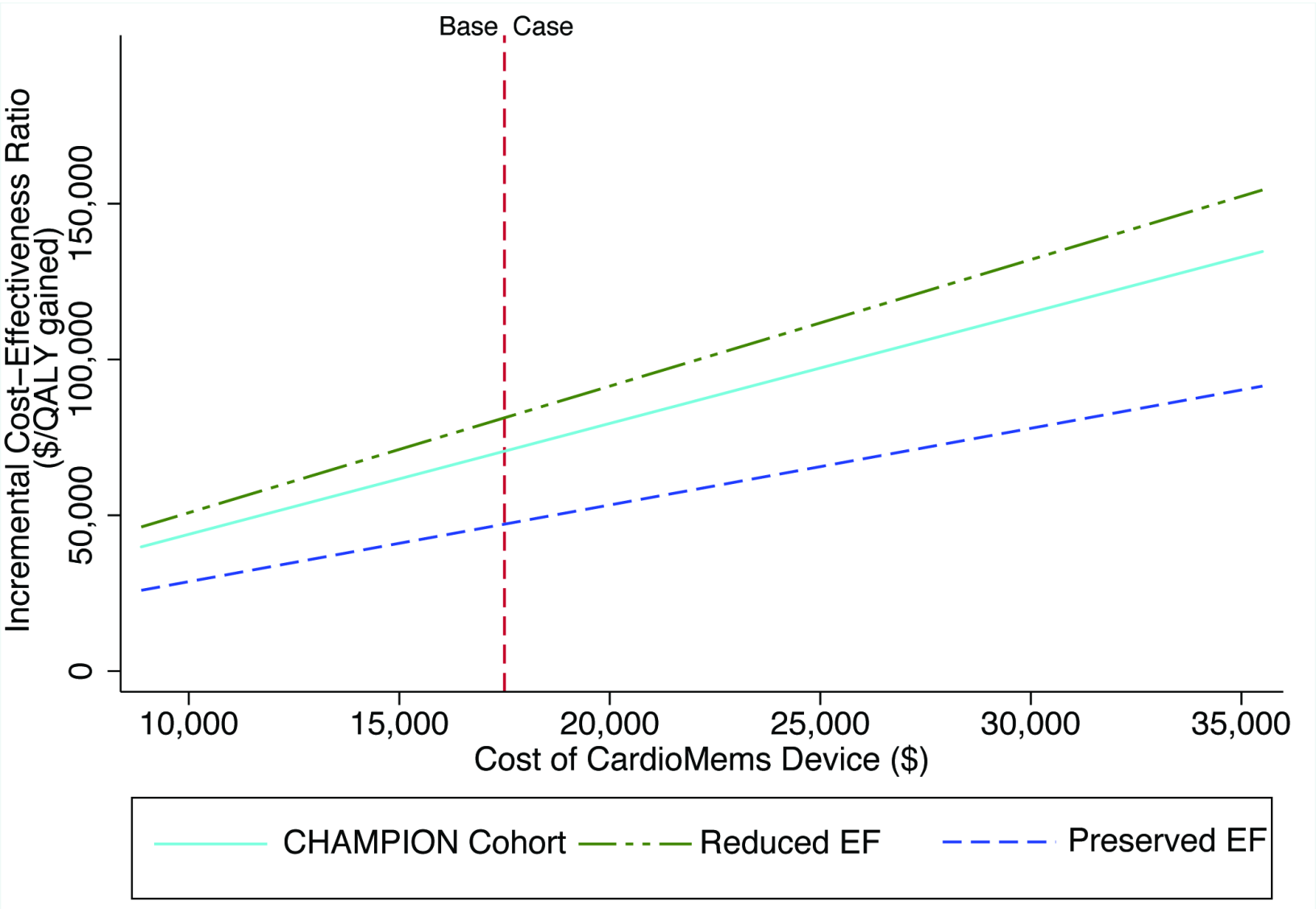
[***] Consists of Medicare professional reimbursement for right-heart catheterization, angiography, and CardioMems placement. CardioMems placement reimbursement not defined; estimated to be equal to a temporary transvenous cardiac electrode placement.

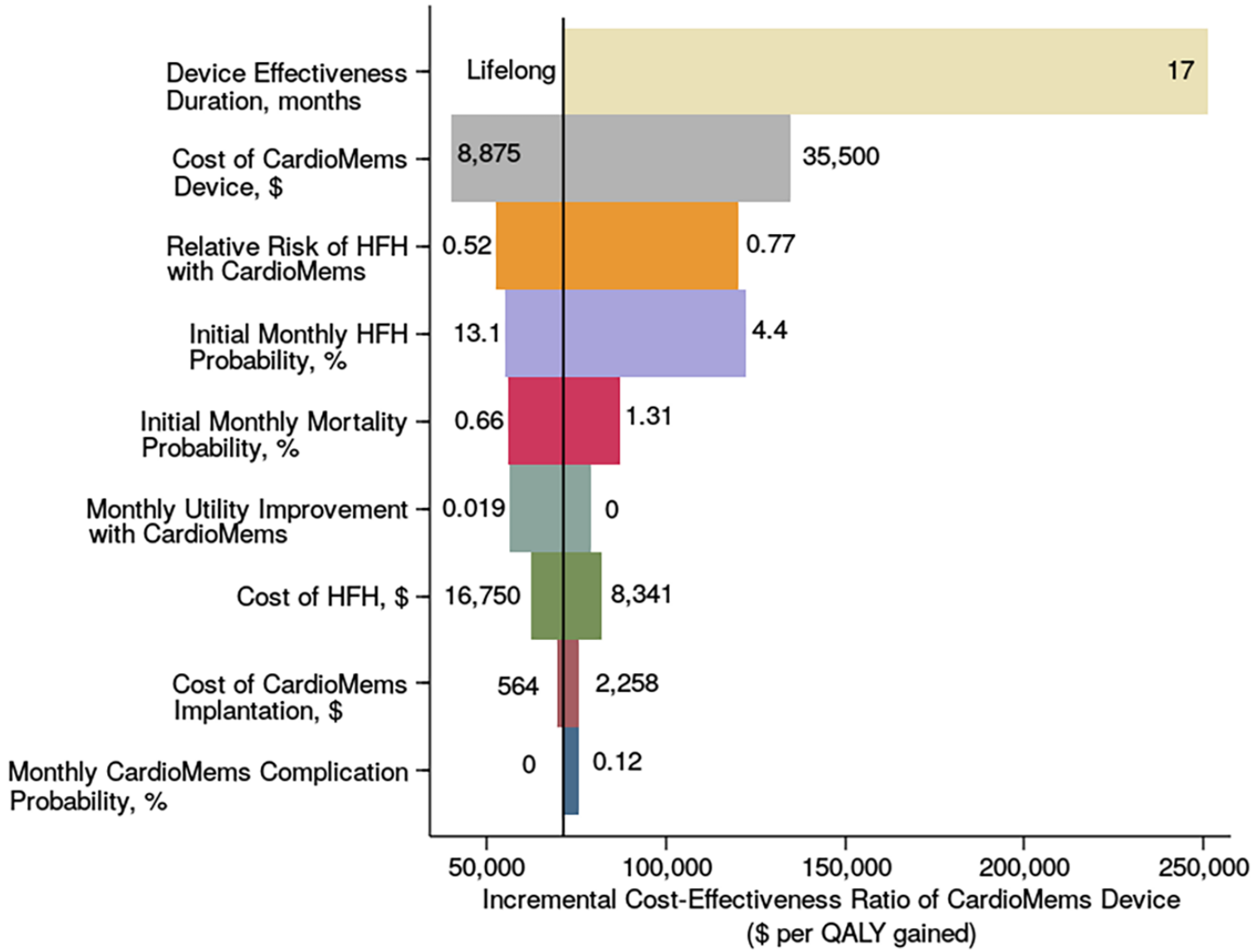
[†††] Estimated secondary to time associated with monitoring program (Dr. Liviu Klein, personal communication, November, 2015) and provider wages (20,21) (see Supplement for details)

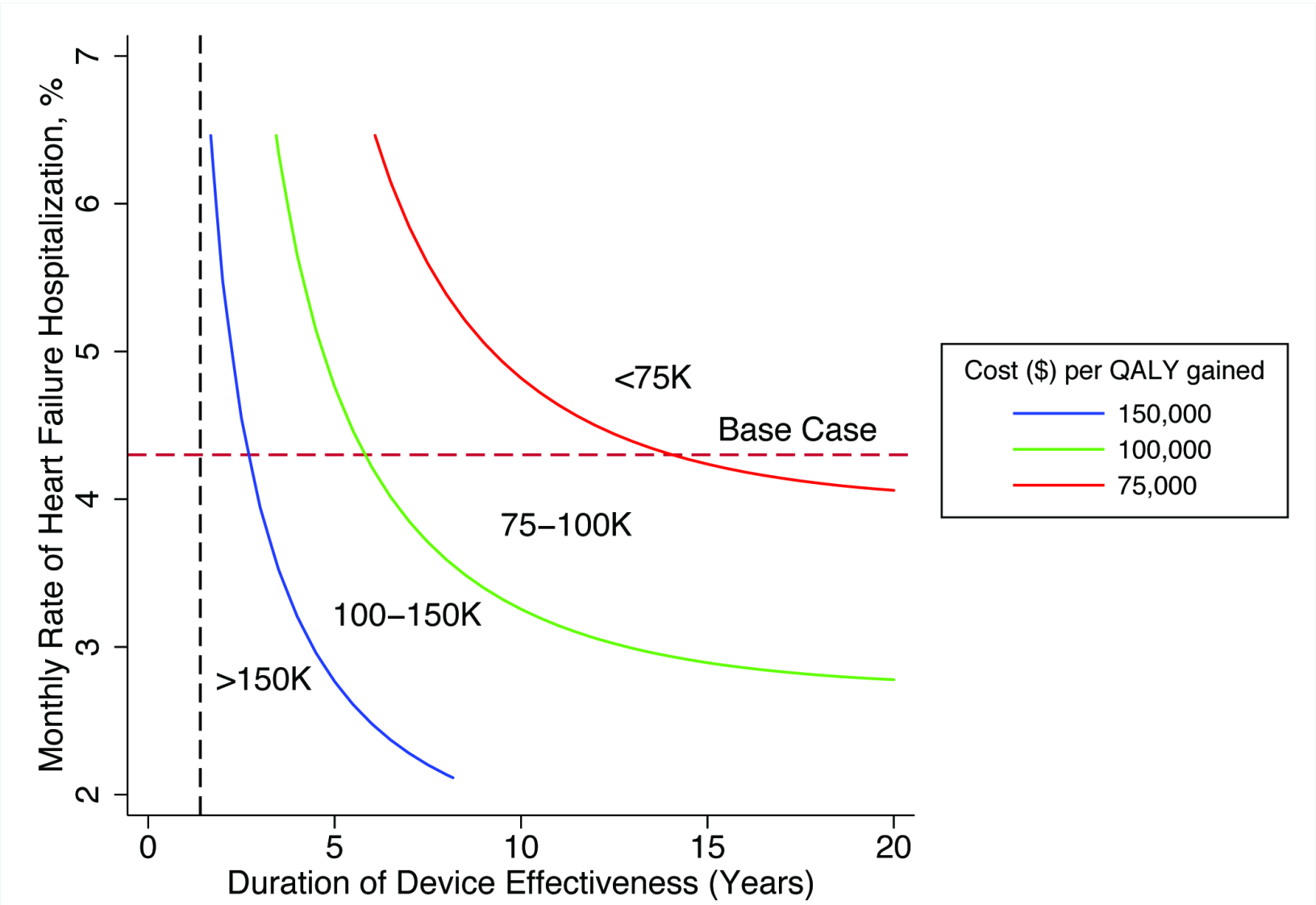
[‡‡‡] MLWHF scores converted into EQ-5D scores.

Table 2. Base Case Results

	Strategy	HFH (# per patient)	Survival (Years)	Cost (2014 USD)	QALY	$/Life Year	$/QALY (ICER)
CHAMPION Cohort	Usual Care	3.12	5.31	156,569	2.46	---	---
	CardioMems	2.18	5.72	176,648	2.74	48,054	71,462
Reduced EF Subgroup	Usual Care	3.10	4.74	148,724	2.18	---	---
	CardioMems	2.31	5.10	168,987	2.43	55,547	82,301
Preserved EF Subgroup	Usual Care	3.17	7.35	184,877	3.48	---	---
	CardioMems	1.74	7.96	204,289	3.88	31,865	47,768


Base Case
Incremental Cost–Effectiveness Ratio ($/QALY gained)
0
50,000
100,000
150,000
10,000
15,000
20,000
25,000
30,000
35,000
Cost of CardioMems Device ($)
CHAMPION Cohort
Reduced EF
Preserved EF


Device Effectiveness Duration, months
Lifelong
17
Cost of CardioMems Device, $
8,875
35,500
Relative Risk of HFH with CardioMems
0.52
0.77
Initial Monthly HFH Probability, %
13.1
4.4
Initial Monthly Mortality Probability, %
0.66
1.31
Monthly Utility Improvement with CardioMems
0.019
0
Cost of HFH, $
16,750
8,341
Cost of CardioMems Implantation, $
564
2,258
Monthly CardioMems Complication Probability, %
0
0.12
50,000
100,000
150,000
200,000
250,000
Incremental Cost-Effectiveness Ratio of CardioMems Device
($ per QALY gained)


Monthly Rate of Heart Failure Hospitalization, %
2
3
4
5
6
7
0
5
10
15
20
Duration of Device Effectiveness (Years)
<75K
Base Case
75–100K
100–150K
>150K
Cost ($) per QALY gained
150,000
100,000
75,000

Cost-Effectiveness of Implantable Pulmonary Artery Pressure Monitoring in Chronic Heart Failure

(Technical Appendix)

Table of Contents

Text:

Heart Failure Hospitalization Rate

The heart failure hospitalization rate was derived from the results of the CHAMPION trial.(1-3) We used the hospitalization frequency of the control arm over the duration of the trial to determine the baseline monthly hospitalization rate. The hospitalization rate was higher in the first six months of the trial compared to later months. This is consistent with evidence that rehospitalization rate decreases as the time from the index hospitalization increases,(4,5) which may be secondary to stabilization of the disease or death of the most ill patients. Therefore, we modeled a decreasing hospitalization risk from the first month to the seventeenth month that was calibrated to both the 6-month and 17-month hospitalization rates in the CHAMPION trial for both arms. Model calibrations were performed simultaneously on the hospitalization rates and the 17-month mortality rate in the CHAMPION trial (see below for further detail on calibration). We used an exponential decrease given the rate of rehospitalization decreases most in the initial months after the first hospitalization,(4,5) and a linear decrease would not allow us to fit the same model to groups with different baseline hospitalization risk. We determined the value of the exponential decrease by calibrating to the CHAMPION trial results. We utilized probabilities in our model. The formula, after calibration, was as follows:

$$\textit{Heart Failure Hospitalization Probability at Month } t = \textit{Baseline Probability} * 0.478^{(t-1)/17}$$

This formula, derived from the best fit of the trial rates, means that the hospitalization probability decreases by approximately 50% from the baseline by month 17. After 17 months, we held the hospitalization rate steady due to the lack of published data in this population post-CHAMPION trial. For stage-specific, cohort-specific monthly hospitalization probabilities refer to Table S2.

Heart failure rehospitalization rates vary substantially in different populations based on both the level of underlying illness and the care received. Therefore, we tested 50% increases and decreases in the baseline hospitalization rate.

All-Cause Mortality Rate

The all-cause mortality rate was taken from the overall mortality of the CHAMPION trial.(1-3) We based the mortality on the number of deaths per person-time over the entire randomized duration of the trial. This was modeled as a baseline all-cause monthly mortality rate and an additional inpatient mortality risk in those hospitalized for heart failure. We modeled an increase in the all-cause monthly mortality rate in those with a heart failure hospitalization during the previous two months. The mortality associated with a heart failure hospitalization was derived from the OPTIMIZE-HF registry.(5) The increase in all-cause mortality after heart failure hospitalization was based on estimates from the literature.(5-7) We estimated this increased relative risk via the ratio between the mortality rate seen in OPTIMIZE-HF patients within 60-90 days of hospitalization and our average monthly mortality rate after adjusting for inpatient heart failure mortality. After the average duration of the trial, we extrapolated an exponential age-related increase in all-cause mortality based on published data,(8) using the following:

$$\textit{All-Cause Mortality Probability} = \textit{Baseline Mortality} * \textit{Annual Change}^{(\textit{Age-Age at the end of the trial})}$$

The annual change was an increase of 2.6% per year in those with reduced ejection fraction and 4.6% per year in those with preserved ejection fraction, who had lower baseline mortality rates. These ejection fraction-specific estimates were based off of a multivariate analysis of 5,419 patients with heart failure with follow-up from 5 to 8 years.(8) The

increase was started after the 17-month trial period; we did not adjust for age over the first 17 months (mean trial follow-up) because heart failure literature suggests mortality rates initially decrease with time from discharge.(7) The age-specific mortality rate from CDC data did not exceed the baseline all-cause mortality used in our model until age 88, at which time there were no survivors in our model.(9) To avoid a survival benefit for those with heart failure in sensitivity analyses at any point, we set the mortality to be the maximum between the national, age-specific mortality and our estimate of all-cause mortality. For age-specific, cohort-specific all-cause mortality probabilities, refer to Table S3.

Reduction in Heart Failure Hospitalizations with CardioMems Device

We estimated the reduction in heart failure hospitalizations with the CardioMems device from the hospitalization hazard rate of the CardioMems arm compared to the control arm in the CHAMPION trial (0.63).(3) Based on the point estimate, we assumed a monthly 37% relative risk reduction of hospitalization between those with and without the device in our main analysis. The upper (0.77) and lower limits (0.52) of the confidence interval of the hazard rate were used in sensitivity analyses to estimate the risk reductions.

In the main analysis, we assumed the CardioMems device would be effective lifelong. We varied this duration in sensitivity analyses. The FDA was presented with 17.4 months of randomized data. Recent data of longer follow-up, including non-randomized open access, is now available up to 31 months.(10) Both of these time points were tested as cut-offs for the duration of effectiveness in sensitivity analyses. After the cut-off, the relative risk of hospitalization was set to 1 and the incremental utility of the device was set to 0. We

primarily analyzed the cost-effectiveness without continued monitoring costs after this cut-off duration. However, in alternative sensitivity analyses in the supplement, we analyzed the cost-effectiveness with continued monitoring costs after the cut-off duration (see below).

Relative Rates for Preserved Ejection Fraction and Reduced Ejection Fraction Subgroups

Baseline rate of hospitalization and mortality for the cohort were transformed into rates for the preserved and reduced ejection fraction subgroups. We used the subgroup-specific rates of hospitalization and all-cause mortality from previous large trials to estimates the relative risk between the two subgroups. We did not use CHAMPION trial data because the small number of patients and events would be less likely to accurately reflect the relative risks between the two groups. For the hospitalization and all-cause mortality rates, we developed relative risk ratios from the patients in the CHARM trials with previous heart failure hospitalization.(4) For the risk of inpatient mortality, we used the OPTIMIZE-HF registry's separate mortality rates for both subgroups.(5)

We used the CardioMems heart failure hospitalization risk reduction specific to preserved ejection fraction (0.48) and reduced ejection fraction (0.67) cohorts.

Hospitalization and Mortality Rates for CHARM Exploratory Analysis

For the CHARM analysis, we used hospitalization and mortality rates from the CHARM-Overall Programme.(11) This included three separate trials with 7,599 patients that investigated the effectiveness of candesartan on patients with heart failure. We used the

combined event rates from the three studies.(11,12) This included 5,421 patients with a previous heart failure hospitalization, of whom 3,346 had reduced ejection fraction and 2,075 had preserved ejection fraction. The mortality rates of those with a previous hospitalization were directly available in the literature.(4) We adjusted these mortality rates to account for the difference in average age with the CHAMPION cohort.(8) The hospitalization rates in the literature were for all patients in the CHARM-Overall Programme. In order to determine rates specific to those with or without a previous heart failure hospitalization and with preserved ejection fraction or with reduced ejection fraction, we used the relative rates of first heart failure hospitalization during the trial between the four groups (preserved ejection fraction with or without previous heart failure hospitalization and reduced ejection fraction with or without previous heart failure hospitalization),(4) the overall hospitalization rate, and the proportion of patients in each group (in the CHARM trials). From this, we were able to estimate specific hospitalization rates for patients with preserved ejection fraction and a previous heart failure hospitalization and those with reduced ejection fraction and a previous heart failure hospitalization. We tested this method by performing it to calculate mortality rates. We found our calculated mortality rates to be within approximately 10% of the rates presented in the literature. However, this estimate was based on the assumption that the relative rate of first rehospitalization between the groups was equal to the relative rate of all rehospitalizations. We modeled the same exponential reduction in hospitalization over a 17-month period as in the CHAMPION trial except for the baseline rates. We also modeled the same inpatient mortality risk and the same relative risk of post-hospitalization mortality. We calibrated the usual care arm to the 37-month (mean follow-up)

hospitalization and mortality rate from the CHARM-trials. For CHARM cohort hospitalization and mortality rates, refer to Tables S2 and S3.

Model Calibration

The CHAMPION cohort parameters were manually calibrated by minimizing the square of the differences between the modeled rates and trial rates in terms of 6-month and 17-month hospitalization rate in the usual care arm, the 17-month mortality rate in the usual care arm, and the difference in hospitalization rates between the two arms at 17 months. Minimization was performed on the sum of squared differences of all four outcomes simultaneously, but the difference in hospitalization differences between the arms was weighed equivalently to the other three parameters combined. We varied the baseline probability of hospitalization, the baseline probability of mortality, and the rate of exponential decline of the hospitalization probability. Calibration was considered complete when optimization did not change any of the variables by more than 1%.

For the CHARM analysis, we calibrated by minimizing the squared differences between the modeled rates and trial rates for 37-month hospitalization and mortality in the usual care arm. Only the usual care arm was calibrated because the CHARM trials did not have patients with the CardioMems intervention. The calibration was performed by varying the baseline probability of hospitalization and the baseline probability of mortality simultaneously. All other variables were held constant from the CHAMPION cohort calibration. Calibration was considered complete when optimization did not change any of the variables by more than 1%.

Event rates were calibrated to the CHAMPION trial results for the CHAMPION cohort.(1-3) Confidence intervals were not available for the hospitalization and mortality probabilities. We were unable to estimate confidence intervals (CI) of the hospitalization rate using a negative binomial distribution because we did not have individual events and event variance. Therefore, we used a Poisson distribution based on the number of events and the duration of follow-up. The data is likely susceptible to over-dispersion and underestimating the range of the confidence interval; however, our calibration estimates approximated the point estimates well and were within the confidence intervals. We utilized the binomial distribution to estimate the 95% confidence intervals of annual mortality probability.

In the CardioMems arm of the CHAMPION trial, there were 84 hospitalizations within 6 months with a hospitalization rate of 0.32 hospitalizations per patient per six months. This indicates a follow-up period of 262.5 six-month periods between the 270 patients. Using the Poisson distribution, the 95% confidence interval was 0.26-0.40. The control arm had 120 heart failure hospitalizations over the first six months for a 6-month rate of 0.44, which means there was a follow-up period of 272.7 6-month periods between the 280 patients. The 95% confidence intervals for this rate would then be 0.36-0.53. Over the entire randomized period, there were 182 heart failure hospitalizations over 395 patient years in the CardioMems arm, which leads to an annual hospitalization rate of 0.46 (CI: 0.40-0.53). There were 279 heart failure hospitalizations over 402.5 patient years in the control arm, which leads to an annual hospitalization rate of 0.69 (CI: 0.61-0.78).

There were 50 deaths in the treatment arm over the duration of the trial, 394.6 patient-years. This translated into an annual mortality rate of 12.7% per patient-year or an annual

probability of death of 11.9% (CI: 8.0%-15.8%). There were 64 deaths in the control arm over the duration of the trial, 402.5 patient-years. This translated into an annual mortality rate of 15.9% per patient-year or an annual probability of death of 14.7%(CI: 10.6%-18.8%).

The CHARM cohort was calibrated to the calculated annual hospitalization and mortality rates of patients in the CHARM trial with previous heart failure admission, which was discussed above.(11) We calibrated to an annual hospitalization rate of 20.1% and an annual mortality rate of 8.5%. Over the mean duration of the CHARM trials (37 months), our model calculated an annual hospitalization rate of 20.2% and an annual mortality rate of 8.6%.

Effect of CardioMems Device on Mortality

We decided to associate hospitalizations with an increased risk of mortality instead of using the trial's point estimate because of substantial uncertainty regarding the device's effect on mortality. The CHAMPION trial was not powered to detect a mortality difference; only 15 patients died during the initial published data with the survival analysis hazard ratio of 0.77 (CI: 0.41-1.54, p=0.45). Initial FDA submission documents included longer-term data with a survival analysis hazard ratio of 0.91 (CI: 0.61-1.34, p=0.62) after 99 total deaths. A later FDA submission with longer follow-up included a survival analysis with a hazard ratio of 0.80 (CI: 0.55-1.15, p=0.23).(2,3) This still only included a total of 114 deaths. We did not calibrate directly to the trial's demonstrated effect on mortality due to the substantial uncertainty regarding this estimate and the low total number of deaths. We assumed the prevented heart failure hospitalizations would be associated with mortality,

both inpatient mortality and an increased risk of post-hospitalization mortality. Therefore, the reduction in heart failure hospitalizations in the CardioMems arm also decreases mortality in the model. In the base case, our model demonstrated an 11.3% relative reduction of the mortality rate over the trial duration of 17 months in the CardioMems arm compared with usual care. In the sensitivity analyses, we tested these assumptions extensively.

First, we analyzed a greater reduction in mortality than in the base case by applying the point estimate from the most recently available survival analysis (20% relative reduction in the risk of mortality). We set the heart failure inpatient mortality and increase in post-heart failure hospitalization mortality to zero and adjusted the baseline mortality rate to keep the undiscounted survival constant in the usual care arm. We then applied a 20% reduction to the monthly mortality rate of the CardioMems arm compared with the usual care arm. This allowed us to reproduce the effect of the trial's mortality hazard rate while keeping the overall survival of the usual care arm constant.

We also performed sensitivity analyses on lower reductions of mortality than in the base case analysis. In each sensitivity analysis, we adjusted the baseline mortality rate to keep the undiscounted survival constant in the usual care arm. First, we assumed that the prevented hospitalizations did not have an increase in post-hospitalization mortality by setting the relative risk of mortality post-hospitalization to 1. In this case, the CardioMems arm had a 5.7% lower mortality rate than the usual care arm. In a second sensitivity analysis, we assumed there was no post-hospitalization increase in mortality and assumed the prevented hospitalizations may be less severe heart failure hospitalizations by decreasing inpatient mortality from 3.9% to 1.9%, which reduced the mortality reduction

to 3.0%. In a third sensitivity analysis, we assumed there was no effect on mortality by setting the inpatient mortality to 0 and the relative risk of mortality post-hospitalization to 1. In this final analysis, the survival of both arms was equal. In each analysis, the undiscounted survival of the usual care arm was equal (75 months).

Additional CardioMems-specific Event Probabilities

Of the 575 patients who underwent right heart catheterization in the CHAMPION trial, 25 were unable to undergo CardioMems implantation.(2) This probability (4.3%) was used as the implantation failure probability. These patients were assumed to have the initial costs of the device and costs of the implantation but did not have the benefits or chronic costs of the device.

There were 8 peri-procedural adverse events of 575 implantation attempts.(1,2) These included hemoptysis, a transient ischemic attack, atypical chest pain, death secondary to sepsis, atrial arrhythmia, arterial embolism, pulmonary artery thrombosis, and sensor not deploying. There were also five major bleeds within one month of the procedure, defined as requiring blood transfusion.(1) These were aggregated to form composite peri-procedural complications during the first month. The sensor not deploying was removed given sensor implantation failure was already considered above and the patient had no further complications. The episode of hemoptysis that was double-counted was also corrected. This led to a periprocedural complication probability of 11/575 (1.9%). There were no serious adverse device events in the randomized period after the initial month. The only non-serious adverse device event reported by the investigator was a patient feeling a "shock" at home.(1,2) The event was determined not to be device/system related by the

clinical events committee. There were also no serious device-related adverse events in the post-trial observational period.(2) Therefore, we decided to set the chronic complication rate, after the initial month, to 0. In sensitivity analyses, we tested the effect of a 0.1% monthly CardioMems complication rate, based on the exact confidence intervals (0-0.7%) for a serious device complications in the first six months after the implant period, during which time there were no complications.(1)

There were no CardioMems sensor failures during the randomized period or the post-trial observational period.(2) We, therefore, assumed a sensor failure rate of 0. In one-way sensitivity analyses, we tested the effect of a monthly 0.12% CardioMems sensor failure probability based on the reported exact Clopper-Pearson confidence interval for sensor failure over the initial 6 months (0-0.7%). We assumed there were no device complications after sensor failure; however, there is limited data given there were no episodes of sensor failure and no complications after the initial peri-procedural time period.

We assumed chronic device complications had no mortality in the main case given there were no device-related deaths. However, given the uncertainty regarding this parameter with no chronic device complications, we performed two-way sensitivity analyses of mortality risk and chronic complication probability (shown below).

The non-heart failure hospitalization rate was taken from the results of the CHAMPION trial.(1) The control arm had a 6-month rate of 0.52 non-heart failure hospitalizations, which was converted to a monthly probability of 8.3%. The same non-heart failure hospitalization was used for the CardioMems arm given the lack of significant difference in non-heart failure hospitalizations between arms.

Utility of Chronic Heart Failure and Heart Failure Hospitalizations

The baseline utility was based on the Minnesota Living with Heart Failure (MLWHF) Questionnaire scores of control patients in the CHAMPION trial at 6 months.(1,2) We utilized the 6-month score instead of the baseline score because the 6-month score was an improvement over the baseline score in both arms, indicating the baseline quality of life measurement may have been negatively influenced by the hospitalization before randomization or the implantation procedure, which both arms underwent. We converted the 6-month quality of life scores into EQ-5D scores using a linear regression estimate from the literature.(13) This regression of EQ-5D scores from MLWHF scores was derived from baseline measurements of patients with NYHA Class III or IV heart failure in the Cardiac Resynchronization in Heart Failure trial.(14) The average MLWHF score of 50.6 in control patients translates to an EQ-5D score 0.553, which was used as the baseline utility in the main analysis for the CHAMPION cohort. In a sensitivity analysis, we used the utility estimate from a predictive multivariate regression using patient characteristics instead of MLWHF scores.(15) The regression was established by regressing EQ-5D data on patient characteristics, including age and NYHA classification, from the Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study trial.(16) Inputting the patient characteristics of the CHAMPION trial mapped to a EQ-5D score of 0.746.

The disutility of a heart failure exacerbation requiring hospitalization was based on a published evaluation of patient utility during and after a heart failure hospitalization.(17) In this study of patients with NYHA Class III or IV heart failure, the health-related quality of life was assessed during hospitalization and six months later. The median value, based on a time-tradeoff, was 0.84 during admission and 0.93 180 days later. This equated to a 10.6%

lower utility during the exacerbation requiring hospitalization. We used a 10.6% lower utility during the hospitalization. We used this to calculate the disutility (-0.059), which we applied for one month. This would be equivalent to a disutility toll of 3.2 days over the month for an acute exacerbation. This was tested in sensitivity analyses, with the disutility toll being varied from 0 days to 6 days.

We performed an alternative analysis of heart hospitalization disutility with estimates of long-term utility dependent on the number of heart failure rehospitalizations.(8) We assumed the change in utility with heart failure rehospitalizations was proportional to baseline utility, which we estimated for our cohort using the multivariate model. In this case, the first rehospitalization decreased utility by 2.9%, the second by an incremental 0.9%, and the third by an additional 2.9%. We used these estimates to calculate utility values over time for each cohort based on the number of heart failure hospitalizations at each time point (Table S5). This led to a longitudinal decrease in utility with increasing heart failure hospitalizations, which was greater in the routine care arm. We applied these as the base utility values over time. In a second analysis, we applied this chronic utility adjusted for heart failure hospitalizations in place of heart failure hospitalization disutility and the incremental value of CardioMems.

Effect of the CardioMems Device on Quality of Life

The CardioMems device was shown to improve quality of life in the CHAMPION trial.(3) The intervention arm was shown to have a statistically significant higher score on the MLWHF score than the control arm. Additionally, this was shown to exist in patients

without a heart failure admission during the trial.(3) This suggests that the CardioMems device improves quality of life independent of its effect on hospitalizations.

In order to model the improvement in quality of life secondary to the CardioMems device, we used a difference-in-difference approach because the baseline MLWHF scores were unequal. We measured the difference from baseline to 6 months in both the CardioMems arm and the usual care arm. We then took the difference (1.2 points) as the improvement secondary to CardioMems. This was converted into an EQ-5D score to estimate the utility benefit (0.010) via the methods discussed previously.(13) The difference in quality of life existed at 6 months in the trial but was no longer statistically significant at 12 months. It is unclear if this is due to a decreased effectiveness over time or fewer follow-up scores measured at 12 months (226 patients without 12 month MLWHF score measurements). The difference between arms in the MLWHF score improvement between baseline and 12 months converted to a 0.004 increase in utility. In the main analysis, we used the 6-month difference-in-difference in utility (0.010) for the first year given the large number of patients that did not complete 12 month scores. After one year, we used the 12-month difference-in-difference in utility (0.004) based on the assumption that the quality of life benefit of the device decreases over time. We conservatively compared the average utility of all patients at baseline compared with all patients with follow-up because the number of missing values at follow-up was substantially greater than the number of deaths.

We tested these assumptions extensively in sensitivity analyses. We tested higher and lower levels of utility benefit secondary to the CardioMems device. First, we used a similar difference in differences model but only used baseline data for patients with 6-month data.

This increased the initial incremental utility (modeled for the first year) of the CardioMems device to 0.025. Second, we used the last observation carried forward imputation of 12-month MLWHF scores. This increased the long-term utility benefit to 0.006. Third, we assumed the utility benefit seen at 6 months was carried forward for the duration of the trial. Finally, we tested if there was no improvement in quality of life independent of the effect on hospitalizations.

The disutility of the CardioMems implantation and the right-heart catheterization was set to 0.5 days, which is equivalent to a toll of -.009 for 30 days, given that it is a short procedure with rapid recovery. In sensitivity analyses, we modeled this ranging from no disutility to one entire day lost.

Additional Disutility Tolls

The disutility of CardioMems complications was assumed to be the disutility of a bleeding event, the most common peri-procedural complication in the CHAMPION trial. In the published literature, this has been estimated to be approximately 0.2 for healthy individuals.(18) This has also been estimated as the disutility of pulmonary embolism, which is another possible complication of the CardioMems device.(19) We thereby assumed CardioMems complications would carry a 20% reduction in patients' utility, which equates to a disutility of -0.111. We applied this disutility for a month in patients with a complication, which would be equivalent to a toll of 6 days. The disutility of a non-heart failure admission was set to be equivalent to a heart failure admission.

Heart Failure Costs

The hospital-level cost of a heart failure hospitalization was based on a published analysis of heart failure hospitalization costs.(20) This study analyzed the discharge data from the 2011 National Inpatient Sample from the Healthcare Cost and Utilization Project, finding the mean cost for all heart failure admissions to be $10,775. We used this cost, inflated to 2014 USD using the medical consumer price index,(21) as the hospital cost in our main case analysis($11,718 after inflation adjustment). The study also contained a multivariate linear regression that estimated the effect of patient and hospital characteristics on the average cost of a hospitalization. In sensitivity analyses, we estimated the cost of a hospitalization in the highest and lowest cost settings based on hospital characteristics, which was adjusted for patient characteristics. Urban hospitals were associated with 12% higher costs compared to rural hospitals; teaching hospitals were associated with 17% higher costs compared to non-teaching hospitals. Hospitals in the Midwest were associated with 19% lower costs than Northeast hospitals. Private hospitals were associated with 13% lower costs than government hospitals. Large hospitals were associated with 8% higher costs than small hospitals. We combined the high cost characteristics and low cost characteristics. The highest-cost hospitals (urban, teaching, government hospitals in the Northeast) would cost 30.5% more than average. The lowest-cost hospitals (rural, non-teaching, private hospitals in the Midwest) would cost 35% less than average.

The costs of a heart failure hospitalization also included the costs of physician care. We estimated these costs using the Medicare physician fee schedule.(22) We utilized the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project

National Statistics on All Stays to ascertain the average duration of stay for patients with heart failure hospitalizations.(23) We used frequency-weighted averages of the length of stay for DRG 291-293 (Heart failure with major complications or comorbidities, with chronic conditions, and without either), leading to an average of 4.8 days. Each patient was assumed to have a primary physician and a consulting cardiologist for the duration of the hospitalization. 80% of patients were assumed to be high complexity and 20% were assumed to be medium complexity. This estimate was approximated based on DRG codes in which 90% of patients had major complications or chronic conditions (DRG 291 or 292) and 10% had neither. We believed that some proportion of those patients with chronic conditions would still be classified as medium complexity. This led to a total cost of $1,114 per hospitalization for physician costs. In the sensitivity analysis on high and low costs of hospitalization, the percentage change in hospital-level costs was also applied to physician-level costs. The hospital-level cost variation represents difference in resource usage during hospitalization and duration of hospitalization, which would also likely affect physician-level costs.

The other medical costs for patients with heart failure were taken from an analysis of lifetime costs in patients with heart failure in Olmstead County.(24) We calculated the monthly outpatient costs per patient. We adjusted these costs for patients with NYHA Class III or IV heart failure derived from a regression model for costs with prevalent heart failure in a model conditional upon survival.(25) The adjusted cost of $606 per month was assumed to be the cost of all outpatient health care for a patient with heart failure at the age of 77 (average age of the patients in Olmstead County study). All hospitalizations costs were accounted for separately. This was adjusted for younger and older patients using a

0.88% increase in cost with each increase in age by one year.(25) For age-specific monthly healthcare costs, refer to Table S7. An additional healthcare cost ($70,224) was modeled at the time of death due to any cause to represent the increase in health care utilization use in the last year before death.(26)

CardioMems Costs

The cost of the CardioMems implantation includes both physician procedural costs and the cost of the device.(27) The procedural cost was estimated using the Medicare fee schedule.(22) This cost included the cost of the right heart catheterization (CPT code 93451), the cost of angiography (CPT code 93568) and the cost of the implantation, which is an unlisted procedure (CPT code 93799).(27) The catheterization cost was $790 and the angiography was $154 based on Medicare reimbursement. The final cost was assumed to be equivalent to inserting a single electrode or pacemaker (CPT code 33210), which would be an additional $185. There was no listed cost available for CPT 93799, which requires description of the procedure to determine pricing. Given that this represents reimbursement for the procedure additional to the cost of right heart catheterization and angiography, we felt this was fairly equivalent to the most simple electrophysiology procedure code. The cost of the device was based on the total operating cost of the device reported to the Center for Medicare and Medicaid of $17,750.(28) Due to substantial uncertainty regarding device price, we tested the effect of changes in the implantation cost of CardioMems from 50% to 200% of the base case in deterministic sensitivity analyses.

The long-term costs of managing the CardioMems device were estimated from the average monthly time required to manage patients with the device by physicians and

nurses and their average wages. We obtained the average monthly time required per patient from a 12-month analysis of managing heart failure patients with the CardioMems device (L. Klein, personal communication, November 2015). We estimated costs using average national wages.(21,29) These estimates also approximated Medicare reimbursement with combined CPT 93297 ($27) and CPT 93299(unlisted; approximately $47) (L. Klein, personal communication, November 2015). Given the uncertainty regarding long-term management and maintenance, we performed threshold analyses of this input cost and cost-effectiveness thresholds ($100,000, and $150,000 per QALY gained). In deterministic sensitivity analyses, we tested the effect of changes in the monthly cost of CardioMems from 50% to 200% of the base case.

The cost of CardioMems-associated complications was estimated to be the cost of a gastrointestinal bleed because bleeding was the most common complication of the trial.(1,2) We calculated a cost of $6,201 using DRG-based Medicare reimbursement for hospital costs and Medicare physician fee schedules to estimate the costs of physician care based on average duration of hospitalization.(22,28) This was comparable to the cost of pulmonary embolism hospitalizations ($6,522), another cause of complication.(22,28)

Additional Costs

Non-heart failure hospitalization costs were estimated as the cost of an admission for pneumonia because this is the most common cause of non-cardiac hospitalizations in patients with heart failure.(30,31) These costs were also calculated using the average DRG-based Medicare reimbursement ($6,844) and costs for physician care ($492) calculated from the Medicare physician fee schedule using the average duration of stay.(22,28)

Probabilistic Sensitivity Analysis

We performed a probabilistic sensitivity analysis to analyze the uncertainty of the model and the cost-effectiveness estimates. We performed 10,000 simulations while sampling parameters simultaneously from their respective distributions (Tables S1, S4, S6). The distributions were generally calculated using the base case as the mean and the range as the 95% confidence interval except as discussed below. We used beta distributions for probabilities and utility values, log-normal distributions for relative risks, and normal distributions for costs.

For most costs, we determined the 95% confidence interval via the relative standard errors (percent of the mean) of the average costs in the national inpatient sample data.(23) We used the same diagnosis-related groups that were used to estimate the base case (discussed above). We assumed the relative standard error was the same for the physician costs of a hospitalization as the relative standard error of the hospitalization costs. The 95% confidence intervals for the costs of monthly outpatient care and the additional costs of the final year of care were directly based on their respective sources.(24,26) The costs of CardioMems implantation and remote monitoring are highly uncertain. Therefore, we estimated the 95% confidence interval to be +/- 50% of the base case estimate.

There were no sensor failure, device complication-related mortality, or device-related adverse events after the peri-procedural period. To estimate the 95% confidence interval of these three variables, we used the Jeffrey's confidence interval.(32)

Probabilistic sensitivity analysis was being performed on the entire cohort. Therefore, we sampled from the baseline event rates but did not sample from the relative risk between ejection fraction subgroups. Additionally, we sampled from the baseline

probability of heart failure hospitalization and did not sample from the stage-related rate of decrease in heart failure hospitalization probability. The cost-effectiveness acceptability curve demonstrates the uncertainty of the model (Figure S5).

Additional Modeling Details

The analysis adopted a societal perspective and discounted healthcare costs and benefits at 3% annually. The only exception is the number of hospitalizations presented in Table 2 (in the accompanying manuscript) is undiscounted. Rates were converted to monthly probabilities, which were utilized in the model. We used Microsoft Excel 2011 (Microsoft, Redmond, Washington), TreeAge Pro 2014 (TreeAge Software, Williamstown, Massachusetts) and STATA 2013 (StataCorp, College Station, Texas) to perform the analysis.

Sensitivity Analyses of Utility Values

All of the model's assumptions were tested with one-way sensitivity analyses including patient utility values. If baseline patient utility were based on the multivariate regression of patient characteristics (utility of 0.746 instead of 0.553), CardioMems would cost $55,521 per QALY gained. If we modeled the chronic utility effect of heart failure hospitalizations, additional to the incremental utility of CardioMems, incremental QALYs increased to 0.30 and the cost per QALY gained would decrease to $66,520. If the chronic utility effect of rehospitalizations replaced acute hospitalization disutility and the incremental benefit of the device in the model, the cost per QALY would increase to $88,600.

If hospitalizations had a greater disutility of -0.11 for a month (equivalent to 6 baseline days instead of 3 baseline days in the main analysis), the device would cost $62,003 per QALY gained. On the other hand, if the disutility were decreased to -0.02 (equivalent to 1 baseline day), the cost would increase to $81,116 per QALY gained.

We also varied the device-related improvement in quality of life. If there were no device-related improvement in quality of life additional to hospitalization reduction, the device would cost $78,910 per QALY gained. If there were an initial improvement that ceases at 12 months, at which time there was no statistically significant difference in MLWHF score, the device would cost $76,494 per QALY. On the other hand, if the quality of life improvement after 12 months is underestimated due to limited follow-up, using the last observation carried forward imputation of utility values (utility improvement of 0.006) after 12 months would generate a cost of $69,144 per QALY gained. If the improvement measured at 6 months (0.010) were carried forward indefinitely, the cost decreased to $65,436 per QALY gained. If we utilize the difference in change from baseline scores for only those with 6-month follow-up (0.025), CardioMems would cost $68,296. Finally, if this higher increased quality of life were life-long, the cost would improve to $51,253.

Sensitivity Analyses of CardioMems Complications

Our sensitivity analyses also included evaluation of device-related complications. If the peri-procedural complication risk increased to 3.06% or decreased to 0.77%, the cost per QALY gained would be $71,715 and $71,209 per QALY gained, respectively. There were no peri-procedural deaths. If there were a peri-procedural death risk of 0.12%, the cost per QALY gained would increase to $71,654. If the placement failure were decreased to 2.68%

or increased to 6.01%, the cost per QALY gained would decrease to $70,300 or increase to $72,665, respectively.

If the monthly chronic complication probability were 0.12%, the device would cost $75,772. If these complications also carried a 20.00% mortality risk, the cost would only increase to $78,818 per QALY gained. If the monthly sensor failure probability were 0.12%, the device would cost $75,970.

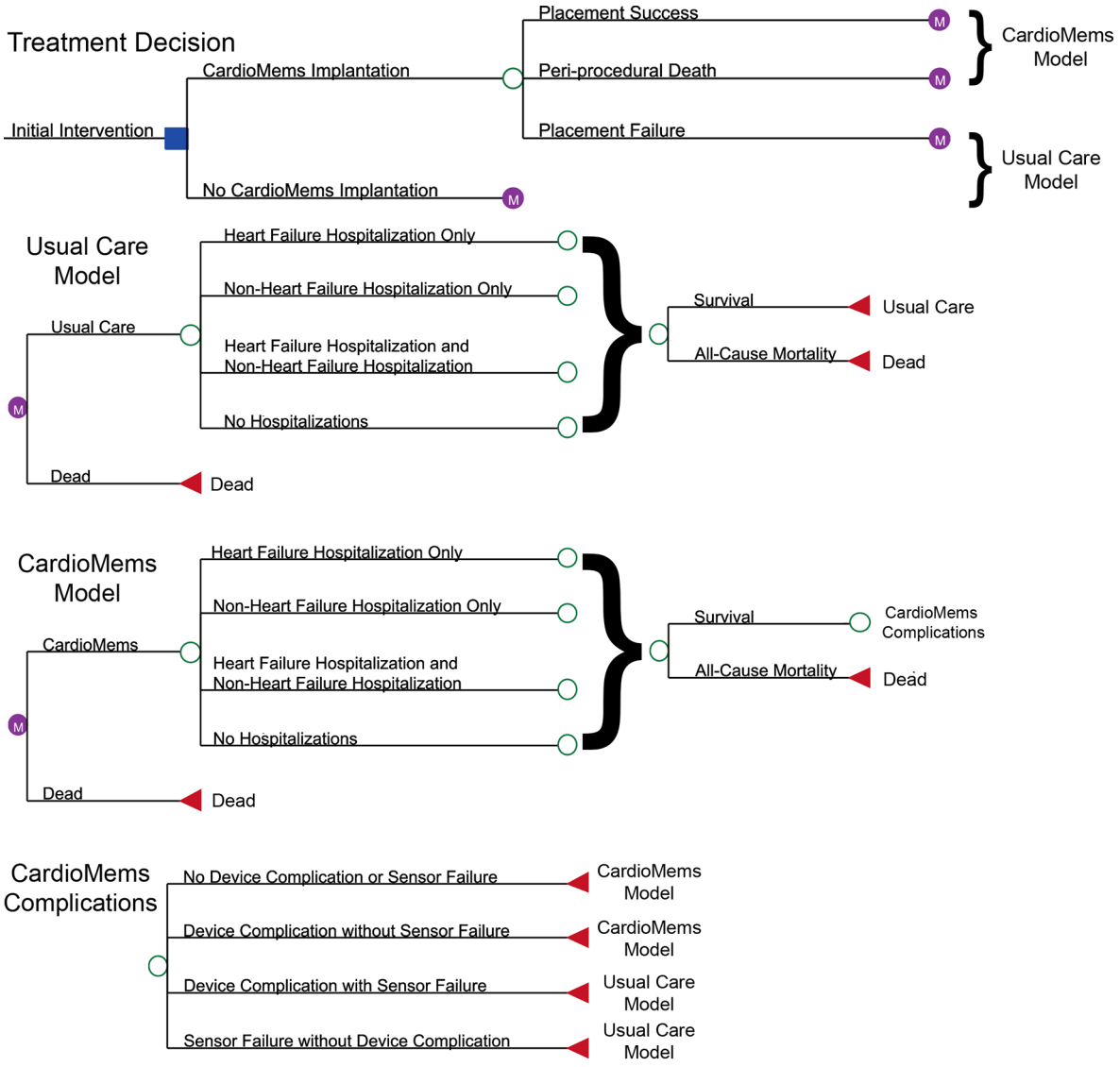
Sensitivity Analyses on Risk of Heart Failure Hospitalization and Mortality

Cohorts of patients with heart failure could have fairly heterogeneous risk of heart failure hospitalization and mortality secondary to differences in the underlying level of illness and, potentially, the medical care received. We tested the effect of changes to the baseline hospitalization and baseline mortality probabilities on the value of the CardioMems device in one and two-way sensitivity analyses. In the base case, we assumed an initial 8.8% monthly risk of heart failure hospitalization (decreasing probability from the first month to month 17), which led to a hospitalization rate of .043 per month and a survival of 5.3 years. Increasing the baseline monthly hospitalization probability to 13.1% (50% increase) led to an increase in the hospitalization rate to .065 per month and a decrease in survival to 4.8 years. In this case, the cost per QALY gained of CardioMems decreased to $55,035. Decreasing the monthly baseline hospitalization probability to 4.4% (50% decrease) led to a decrease in the hospitalization rate to .021 per month and an increase in the average survival to 5.9 years. This increased the cost per QALY gained of CardioMems to $122,292. Increasing the baseline mortality probability to 1.31% decreased average survival to 4.4 years and increased the cost per QALY gained to $87,244.

Decreasing the mortality probability to 0.66% increased the average survival to 6.8 years and decreased the cost per QALY gained to $55,776. We demonstrate the effects of changes to both survival and hospitalization rates Figure S2 by varying the baseline hospitalization and mortality risks simultaneously.

Figures

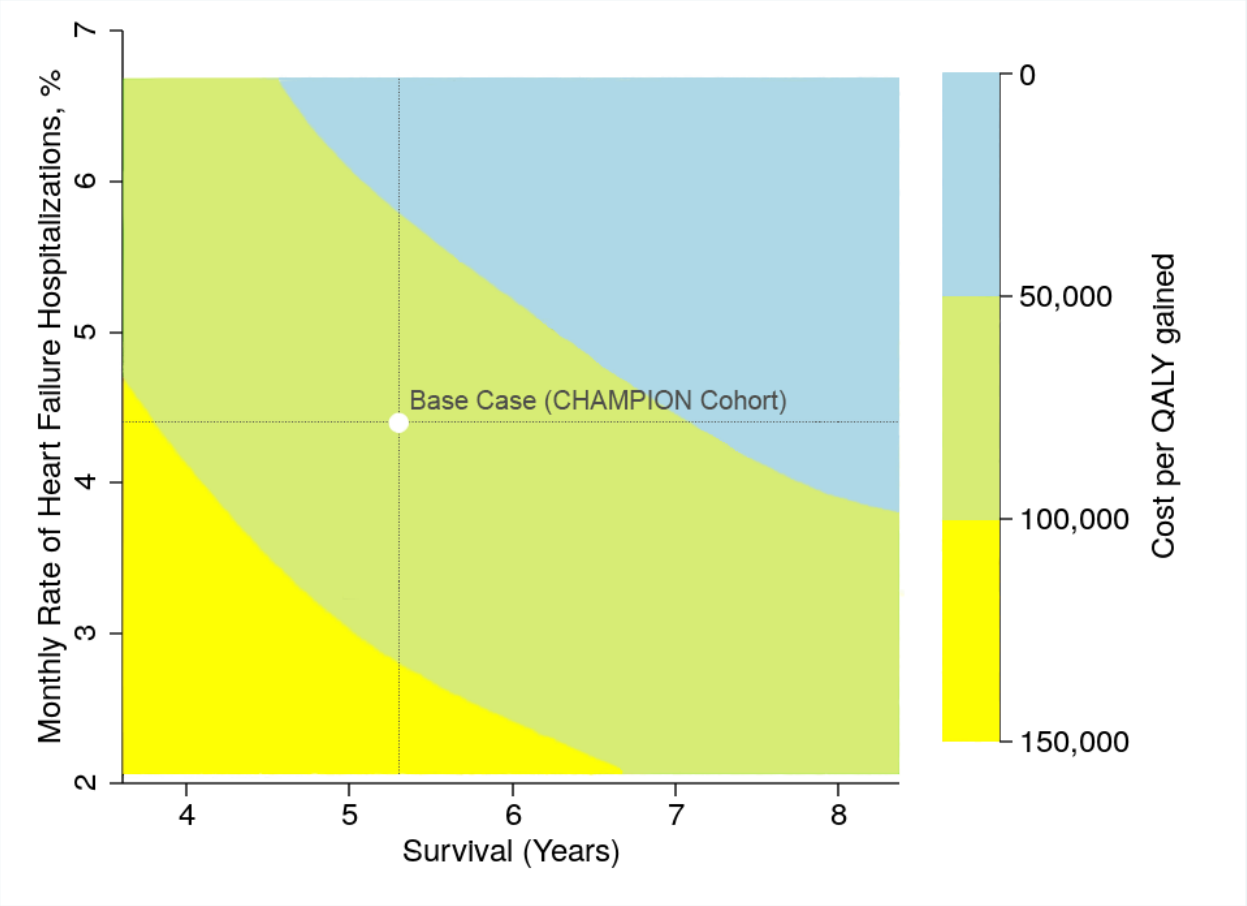
Figure S1: Decision Model Schema



The treatment decision was whether to implant the CardioMems device. This could result in a successful implantation, a failed implantation, or a peri-procedural death. "M" represents a Markov process. Those who had a successful implantation entered the "CardioMems Model" in the "CardioMems" health state. Those with a failed implantation and those who did not undergo CardioMems implantation entered the "Usual Care Model"

in the “Usual Care” health state. Triangles represent the health state a patient entered in the following cycle. Each month, individuals in the “CardioMems” and “Usual Care” states were at risk for both a heart failure hospitalization and a non-heart failure hospitalization. Those in the “Usual Care” state subsequently died or returned to the “Usual Care” state in the next cycle. Those who survived in the “CardioMems” state were also at risk for “CardioMems Complications,” which include device complication and sensor failure. Those who experienced sensor failure entered the “Usual Care” model in the following cycle.

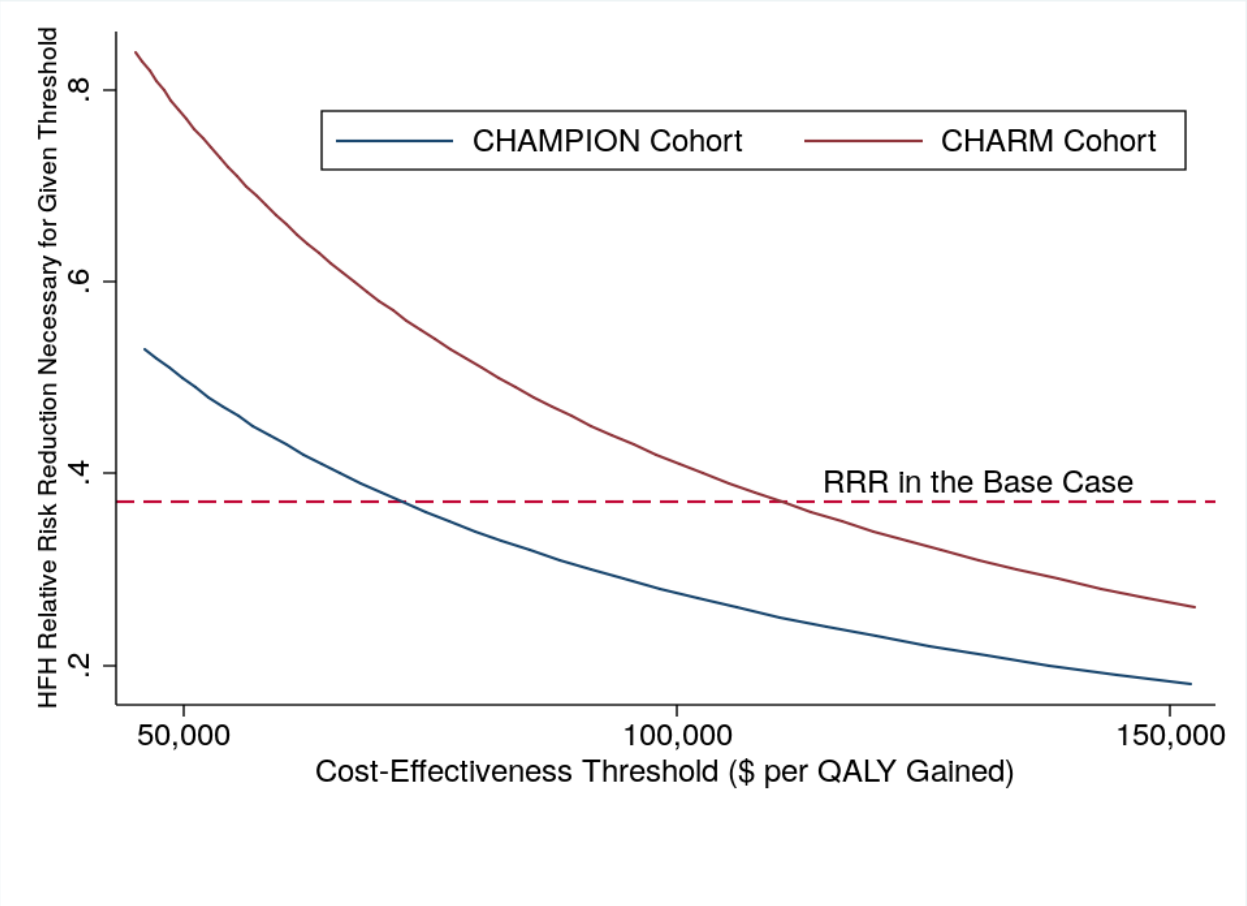
Figure S2. Incremental Cost-effectiveness Ratio of CardioMems Device as a Function of Hospitalization Risk and Survival



This is a two-way sensitivity analysis of the effect of varying the hospitalization and all-cause mortality rates. On the y-axis is the average monthly rate of hospitalization over the patient's lifetime in the usual care arm. On the x-axis is the average survival of the usual care arm. Both are discounted. The colors in the graph represent the cost per QALY gained for patients with the given hospitalization rate and average survival. This graph demonstrates that the cost per QALY gained increased with lower hospitalization rates and decreased survival. However, the device cost did not cross the $150,000 per QALY threshold. The horizontal and vertical lines are the average hospitalization rate (4.3%) and

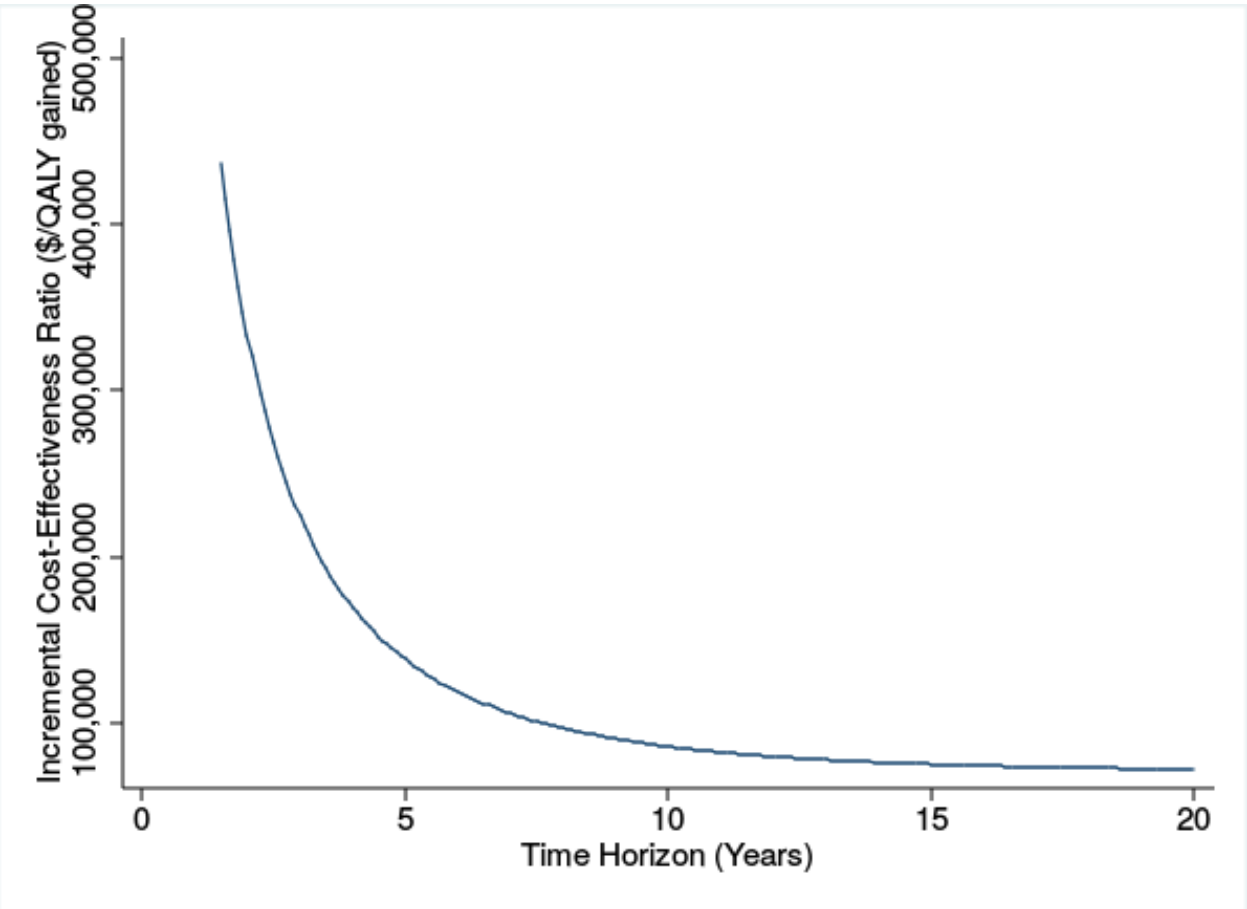
average survival (5.3 years), respectively, of the usual care arm in the base case with the white circle being the cost-effectiveness of the CHAMPION trial cohort.

Figure S3. HFH Relative Risk Reduction for Given Cost-Effectiveness Thresholds



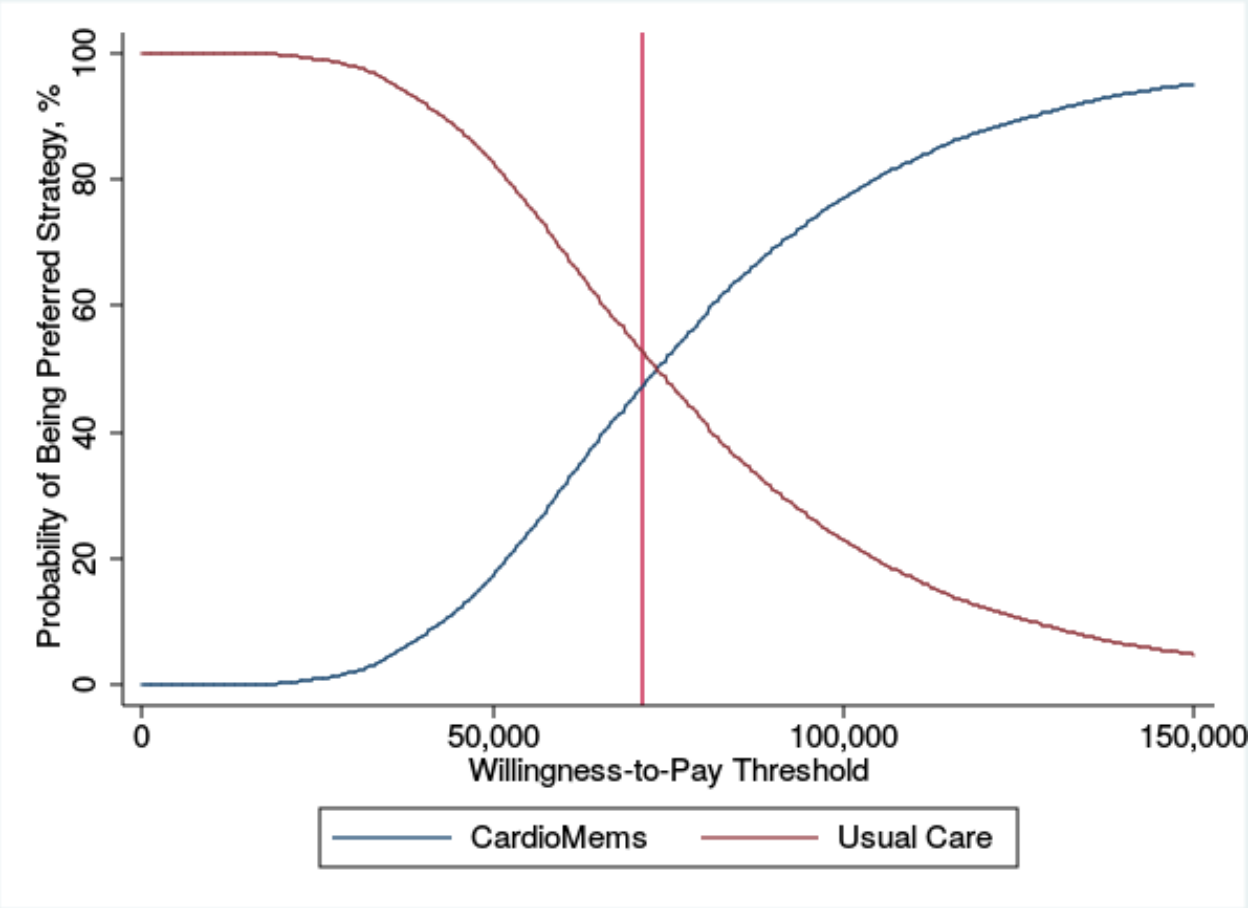
This graph compares the value provided by the CardioMems device in the CHAMPION cohort compared to a lower risk cohort (CHARM cohort). The curves represent the HFH relative risk reduction needed (y-axis) to achieve a given cost-effectiveness threshold (x-axis). The red-dotted horizontal line represents the heart failure hospitalizations risk reduction in the base case (0.37). The CHARM cohort requires a greater reduction in heart failure hospitalizations for any given cost-effectiveness threshold than the CHAMPION cohort.

Figure S4. One-way Sensitivity Analysis of Time Horizon



This curve represents the incremental cost-effectiveness ratio of the CardioMems device as a function of the time horizon used in the model. In the base case, we used a lifelong time horizon. The cost per QALY gained of CardioMems decreases sharply as the time horizon increases from the randomized trial duration (17 months).

Figure S5. Cost-Effectiveness Acceptability Curve***



This curve demonstrates the percentage of 10,000 simulations in which CardioMems therapy or usual care is the preferred strategy at given willingness-to-pay thresholds.

Tables

Table S1. Transition Probabilities (Monthly)[*†]

Probability Parameter	Base Case	95% CI	Distribution[‡]	Source
CHAMPION cohort				
Baseline All-Cause Mortality (%)[§**]	0.99	0.66-1.31	Beta	(1-3)
Baseline Heart Failure Hospitalization (HFH)(%)[††]	8.76	4.38-13.15	Beta	(1-3)
Inpatient HFH Mortality (%)	3.90	3.60-4.20	Beta	(33,34)
Relative Risk of Death after HFH[‡‡]	3.32	1.00-4.98	Log-Normal	(35)
Non-Heart Failure Hospitalization (%)	8.30	6.99-9.60	Beta	(1-3)
Relative Risk (RR) of Preserved Ejection Fraction (pEF) Subgroup, compared to Reduced Ejection Fraction (rEF) Subgroup				
RR of All-Cause Mortality, pEF vs. rEF	0.52	0.43-1.00	---	(4,5,7,36)
RR of HFH, pEF vs. rEF	0.64	0.54-1.00	---	(4,5,7,36)
RR of HFH Inpatient Mortality, pEF vs. rEF	0.74	0.67-1.00	---	(4,5,7,36)
CHARM Cohort[§§]				
Heart Failure Mortality (%)[***]	0.66	0.43-0.89	Beta	(4,11,12)
Baseline HFH (%)[***,††]	3.11	2.32-3.89	Beta	(4,11,12)
CardioMems Arm Specific Parameters				
RR of HFH, compared to usual care (both arms)	0.63	0.57-0.80	Log-Normal	(1-3)
RR of HFH, rEF	0.67	0.54-0.83	Log-Normal	(1-3)
RR of HFH, pEF	0.48	0.30-0.76	Log-Normal	(1-3)
Placement Failure (%)	4.35	2.68-6.01	Beta	13,14
Periprocedural Death (%)[†††]	0	0-0.44	Beta	(1,2)
Periprocedural Complication (%)[‡‡‡]	1.91	0.77-3.06	Beta	(1,2)
Chronic Device Complications (%)[†††]	0	0-0.03[§§§]	Beta	(1,2)
Mortality Risk from a Chronic Device Complication (%)[†††]	0	0-20.00	Beta	(1,2,37)
Sensor Failure (%)[†††]	0	0-0.03[§§§]	Beta	(1-3)

[*] Abbreviations: CI: confidence interval; PSA: probabilistic sensitivity analysis; HFH: heart failure hospitalizations; RR: relative risk; pEF: preserved ejection fraction; rEF: reduced ejection fraction; MLWHF: [†] Baseline probabilities refer to the probabilities for patients with reduced ejection fraction. Preserved ejection fraction probabilities calculated via the relative rates between preserved ejection fraction and reduced ejection fraction groups.

‡ Distributions were calculated using the base case as the mean 95% confidence interval. The relative risk of events in the routine care arm between pEF and rEF was not included in the PSA because the PSA was performed for a combined cohort and overall event rates were varied.

§ Estimated from CHAMPION trial control arm

** Adjusted for age with an exponential model (see Table S3)

†† Heart failure hospitalization probability adjusted by a monthly decreasing exponential model based on model stage to adjust for decreasing hospitalization rate with increasing time from initial hospitalization. This was calibrated to 6 months hospitalization rate and 17 month hospitalization rate (mean duration of CHAMPION trial) and set as constant after 17 months (see Table S2)

‡‡ Increased risk for two months prior to returning to baseline

§§ Only differed from CardioMems with regards to hospitalization probability, mortality probability, and baseline quality of life. Used same exponential models.

*** Estimated from patients from all three CHARM trials and adjusted for those with a previous HFH and ejection fraction composition.

††† Given no trial events, base case event probability of 0. Jeffreys confidence intervals were calculated and the beta distribution was applied.

‡‡‡ Includes both procedure-related complications and serious bleeding events (required blood transfusion) in the first month after implantation.

§§§ In deterministic sensitivity analyses, we utilized reported Clopper-Pearson confidence intervals (0-0.12%).

Table S2. Monthly Heart Failure Hospitalization Probability by Cohort and Stage in the Usual Care Arm.

Month	CHAMPION	Reduced EF	Preserved EF	CHARM
1	0.081	0.088	0.058	0.031
2	0.078	0.084	0.055	0.030
3	0.074	0.080	0.053	0.029
4	0.071	0.077	0.051	0.027
5	0.068	0.074	0.049	0.026
6	0.065	0.071	0.047	0.025
7	0.063	0.068	0.045	0.024

8	0.060	0.065	0.043	0.023
9	0.057	0.062	0.041	0.022
10	0.055	0.059	0.039	0.021
11	0.053	0.057	0.037	0.020
12	0.050	0.054	0.036	0.019
13	0.048	0.052	0.034	0.018
14	0.046	0.050	0.033	0.018
15	0.044	0.048	0.031	0.017
16	0.042	0.046	0.030	0.016
17*	0.041	0.044	0.029	0.016

* After month 17, hospitalization risk was held constant.

Table S3. Monthly Baseline All-Cause Mortality Probability by Cohort and Age*

Age	CHAMPION	Reduced EF	Preserved EF*	CHARM
62	0.009	0.01		0.006
63	0.009	0.01		0.006
64	0.009	0.011		0.006
65	0.009	0.011		0.006
66	0.01	0.011	0.005	0.006
67	0.01	0.011	0.005	0.007
68	0.01	0.012	0.005	0.007
69	0.01	0.012	0.006	0.007
70	0.011	0.012	0.006	0.007
71	0.011	0.013	0.006	0.007
72	0.011	0.013	0.006	0.008
73	0.012	0.013	0.007	0.008
74	0.012	0.014	0.007	0.008
75	0.012	0.014	0.007	0.008

* Patients with preserved EF had a mean age of 66, so the risk of the cohort was calculated with probabilities starting at this age.

Table S4. Utility Inputs*†

Utility Parameter	Point Estimate	95% CI	PSA Distribution	Source
Baseline Utility, CHAMPION Cohort‡	0.553	0.512-0.746	Beta	(1-3,13)
Baseline Utility, CHARM Cohort‡	0.661	0.643-0.679	Beta	(13,38)
Disutility of Heart Failure Hospitalization	0.059	0-0.012	Beta	(17)
Disutility of Non-Heart Failure Hospitalization	0.059	0-0.012	Beta	(17)
Utility of CardioMems Device for first 12 months‡	0.010	0-0.019	Beta	(1-3,13,17)

Utility of CardioMems Device after first 12 months‡	0.004	0-0.019	Beta	(1-3,13,17)
Disutility of CardioMems Placement	0.001	0-0.019	Beta	Assumed
Disutility of CardioMems Complication	0.111	0.055-0.166	Beta	(18,19)

* Abbreviations: CI: confidence interval; PSA: probabilistic sensitivity analysis.

† All disutilities are negative utility values with duration of one month.

‡ MLWHF scores converted into EQ-5D scores.

Table S5. Chronic Utility Modeled as a Function of Heart Failure Hospitalizations

Time from Start of Model (Years)	CardioMems Arm Utility	Routine Care Arm Utility
0	0.553	0.553
0.5	0.549	0.546
1	0.545	0.541
1.5	0.543	0.538
2	0.541	0.536
2.5	0.54	0.536
3	0.538	0.535
3.5	0.537	0.534
4	0.536	0.534
4.5	0.536	0.533
5	0.536	0.533
5.5	0.535	0.532
6	0.535	0.53
6.5	0.535	0.529
7	0.534	0.528
7.5	0.534	0.526
8	0.534	0.525
8.5	0.534	0.524
9	0.534	0.523
9.5	0.533	0.523
10	0.533	0.522
10.5	0.533	0.521
11	0.533	0.52
11.5	0.533	0.52
12	0.533	0.519
12.5	0.533	0.519
13	0.532	0.518
13.5	0.532	0.518
14	0.532	0.518
14.5	0.532	0.517
15	0.532	0.517
15.5	0.532	0.517
16	0.532	0.516
16.5	0.531	0.516
17	0.531	0.516
17.5	0.531	0.516
18	0.531	0.516

18.5	0.531	0.515
19	0.531	0.515
19.5	0.531	0.515
20	0.531	0.515

Table S6. Cost Inputs*

Cost Parameter*	Point Estimate†	95% CI	PSA Distribution	Source
Monthly Outpatient Medical Care‡	531	453-609	Normal	(24)
Cost of Heart Failure Hospitalization§	12,845	12,552-13,138**	Normal	(20),(22)
Cost of CardioMems Device	17,750	8,875-26,625††	Normal	(28)
Cost of CardioMems Placement	1,129	565-1,694††	Normal	(27,28)
Monthly Cost of CardioMems Device Management	68	34-102††	Normal	(27)
Cost of CardioMems Complication	6,201	6,037-6,365	Normal	(22,28)
Cost of Non-Heart Failure Hospitalization§	7,336	6,988-7,684	Normal	(22,28)
Additional Costs of Last Year of Life	70,224	68,138-72,310	Normal	(26)

* Abbreviations: CI: confidence interval; PSA: probabilistic sensitivity analysis.

† Costs in 2014 USD.

‡ Varies by age (See Table S7).

§ Includes cost of hospital costs and physician costs.

** In deterministic sensitivity analyses, we tested an alternative range of heart failure hospitalization costs ($8,341-$16,750) based on hospital characteristics due to the heterogeneity of heart failure cohorts in different clinical settings.

†† In deterministic sensitivity analyses, we utilized 50%-200% of the base case due to uncertainty of CardioMems-related costs.

Table S7. Outpatient Costs by Age*

Age	Cost ($)
60	522
61	527
62	531
63	536
64	541
65	546
66	550
67	555
68	560
69	565

70	570
71	575
72	580
73	585
74	590
75	595
76	601
77	606
78	611
79	617
80	622

* All costs presented in 2014 USD.

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